REMARKS

The Amendments

Claims 1, 3, 10-21, 30 and 31 are pending. Claims 10-12 have been cancelled. Claims 1, 3, 13-21, 30 and 31 have been amended. New claims 32-34 have been added. Accordingly, claims 1, 3, 13-21, and 30-34 are now pending in this application.

Independent claim 1 has been amended to recite "[a] chemically modified nucleic acid molecule, wherein: a) the nucleic acid molecule comprises a sense strand and a separate antisense strand, each strand having one or more pyrimidine nucleotides and one or more purine nucleotides; b) each strand of the nucleic acid molecule is independently 18 to 27 nucleotides in length; c) an 18 to 27 nucleotide sequence of the antisense strand of the nucleic acid molecule is complementary to a human intercellular adhesion molecule (ICAM) RNA sequence comprising SEQ ID NO: 439; d) an 18 to 27 nucleotide sequence of the sense strand of the nucleic acid is complementary to the antisense strand and comprises an 18 to 27 nucleotide sequence of the human ICAM RNA sequence; e) about 50 to 100 percent of the nucleotides in the sense strand and about 50 to 100 percent of the nucleotides in the antisense strand are chemically modified with modifications independently selected from the group consisting of 2′-O-methyl, 2′-deoxy-2′-fluoro, 2′-deoxy, phosphorothioate and deoxyabasic modifications; and f) one or more of the purine nucleotides present in one or both strands of the nucleic acid molecule are 2′-O-methyl purine nucleotides and one or more of the pyrimidine nucleotides present in one or both strands of the nucleic acid molecule are 2′-deoxy-2′-fluoro pyrimidine nucleotides." Support for the amendment can be found at, *inter alia*, page 8, line 3; page 9, lines 13-27; page 12, lines 21-30; page 13, lines 8-17; page 14, lines 11-16; page 17, lines 1-7; page 31, lines 16-31; and Tables I and II, and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/363,124 (*see, e.g.*, page 3, lines 15-17; page 5, line 13, to page 15, line 9; page 12; lines 4-7, and 1-15; page 18, lines 1-5; page 19, lines 11-14; page 20, lines 16-20; page 21, lines 3-6; page 25, lines 17-29; page 32, lines 11-12; page 36, line 1, to page 37, line 31; page 372, entry in Table III; and page 425); 60/409,293 (*see, e.g.*, page 35, lines 9-29; page 19, lines 20-29; and page 20, lines 1-10); 60/440,129 (*see, e.g.*, page 12, lines 1-20); and 60/358,580 (*see, e.g.*, page 3, lines 16-19; page 5, lines 13-16; page 8, lines 9-18; page 10, lines 7-12; and page 11, lines 27-30).

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Support for amended claim 3 can be found at, *inter alia*, page 16, lines 6-8; and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/363,124 (*see, e.g.*, page 15, lines 3-9); and 60/358,580 (*see, e.g.*, page 5, lines 1-4, and page 23, lines 5-7).

Support for amended claim 13 can be found at, *inter alia*, page 17, lines 7-9; and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/363,124 (*see, e.g.*, page 10, lines 3-27; page 11, lines 8 and 22); 60/440,129 (*see, e.g.*, page 15, lines 14-20, and page 10, lines 10-13); and 60/358,580 (*see, e.g.*, page 10, lines 7-9).

Support for amended claim 14 can be found at, *inter alia*, page 17, lines 7-15; page 22, lines 21-23; and page 40, lines 10-20; and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/363,124 (*see, e.g.*, page 6, lines 14-15); 60/440,129 (*see, e.g.*, page 22, lines 1-9, and page 10, lines 13-17).

Support for amended claim 15 can be found at, *inter alia*, page 17, lines 7-9; page 22, lines 23-31; and page 40, lines 1-9; and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/363,124 (*see, e.g.*, page 10, lines 3-16, and page 11, lines 1-11, and 22); 60/440,129 (*see, e.g.*, page 15, lines 14-20, and page 10, lines 10-13); and 60/358,580 (*see, e.g.*, page 10, lines 7-10).

Support for amended claim 16 can be found at, *inter alia*, page 17, lines 21-27; page 23, lines 1-4; page 43, lines 2-5; and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/363,124 (*see, e.g.*, page 10, lines 3-16, and 20-21; page 11, lines 1-11; page 40, lines 1-18); 60/440,129 (*see, e.g.*, page 16, lines 19-25, and page 21); and 60/358,580 (*see, e.g.*, page 10, lines 2-3, and 7-12, and page 35, lines 1-15).

Support for amended claim 17 can be found at, *inter alia*, page 17, lines 27-28, and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/363,124 (*see, e.g.*, page 5, line 16;

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page 14, lines 10-13; page 40, lines 4-18); 60/440,129 (*see, e.g.*, page 20, lines 1-5); and 60/358,580 (*see, e.g.*, page 35, lines 5-7).

Support for amended claim 18 can be found at, *inter alia*, page 17, lines 15 and 16, and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/363,124 (*see, e.g.*, page 10, lines 3-16, and page 11, lines 1-11, and 22); 60/440,129 (*see, e.g.*, page 15, lines 4-20, and page 10, lines 10-13); and 60/358,580 (*see, e.g.*, page 10, lines 7-10, and page 11, lines 1-4).

Support for amended claim 19 can be found at, *inter alia*, page 17, lines 15-17, page 22, lines 25-32, and elsewhere in the specification as filed. Support is also found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/363,124 (*see, e.g.*, page 6, lines 14-15); 60/440,129 (*see, e.g.*, page 22, lines 25-30, and page 10, lines 13-17); and 60/358,580 (*see, e.g.*, page 10, lines 29-31).

Support for amended claim 20 can be found at, *inter alia*, page 17, lines 30-31, page 18, lines 21-26, and elsewhere in the specification as filed. Support is also found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/363.124 (*see, e.g.*, page 6, lines 14-15); 60/440,129 (*see, e.g.*, page 23, lines 15-20, and page 10, lines 13-17); and 60/358,580 (*see, e.g.*, page 10, lines 3-5).

Support for amended claim 21 can be found at, *inter alia*, page 18, lines 12-13 and page 23, lines 4-6, and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/363,124 (*see, e.g.*, page 9, lines 24-25; page 10, lines 31, to page 11, lines 11); 60/440,129 (*see, e.g.*, page 24, lines 13-18); and 60/358,580 (*see, e.g.*, page 9, lines 24-33).

Support for amended claim 30 can be found at, *inter alia*, page 23, lines 7-8, and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/363,124 (*see, e.g.*, page 8, line 26, to page 9, line 13); 60/440,129 (*see, e.g.*, page 13, lines 16-25); and 60/358,580 (*see, e.g.*, page 9, lines 5-13).

Support for amended claim 31 can be found at, *inter alia*, page 24, lines 30-31; and elsewhere in the specification as filed. Support can also be found in the priority documents, such

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as, for example, in U.S. Provisional patent application Nos. 60/363,124 (*see, e.g.*, page 18, lines 15-20); and 60/358,580 (*see*, e.g., page 16, lines 30-31).

Support for new claim 32 can be found at, *inter alia*, page 40, lines 21-29; page 43, lines 11-14, and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/440,129 (*see, e.g.*, page 25, lines 20-25; page 10, lines 13-17); and 60/358,580 (*see, e.g.*, page 10, lines 14-16).

Support for new claim 33 can be found at, *inter alia*, page 12, lines 16-20, page 43, lines 5-9, and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/363,124 (*see, e.g.*, page 4, lines 9-11; page 9, lines 5-13); and 60/358,580 (*see, e.g.*, page 9, lines 9-10).

Support for new claim 34 can be found in the specification at, *inter alia*, page 25, lines 21-27, page 43, lines 7-9, and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application No. 60/363,124 (*see, e.g.*, page 4, lines 9-11; page 5, lines 13-22; and page 9, lines 5-13).

Amendments to and cancellations of the claims are made without prejudice or disclaimer, and do not constitute amendments to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments or cancellations are not an admission regarding the patentability of subject matter of the amended or canceled claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and Applicant respectfully requests their entry.

Claim objection

Claim 1 has been objected to for lacking an underline under the term "a" prior to the phrase "nucleotide sequence." which would otherwise indicate the change that had been introduced into that claim in the last amendment and response filed on December 8, 2005. With the present submission, this claim has been amended to render the objection moot. Applicant thus respectfully requests its withdrawal.

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Information Disclosure Statement

The Information Disclosure statement filed on October 3, 2005, was objected to for allegedly failing to comply with the provisions of 37 CFR 1.98(b)(5). Specifically, the information referred to as GenBank Accession Nos. at pages 20-23 was not considered because a publication date was not provided. Without acquiescing to the Office's contentions, and solely in the interest of expediting prosecution, Applicant hereby submits herewith a Third Supplemental Information Disclosure statement and SB08 form containing a re-listing of all of the GenBank Accession numbers with publication dates. The Commissioner is authorized to deduct the fee associated with the Third Supplemental Information Disclosure Statement from Deposit Account No. 13-2490. Copies of the references have not been attached because the Office already has copies.

Claim Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1, 3, 10-21, 30, and 31 were rejected under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. Specifically, the Office alleged that "the scope and meaning of the limitation 'a human huntingtin (ICAM) nucleotide sequence comprising SEQ ID NO:439' is ... unclear." Office Action, at page 4. As discussed above, Claim 1 has been amended to such that it no longer recites "a human huntingin (ICAM) nucleotide sequence comprising SEQ ID NO: 439," instead, it recites "a human intercellular adhesion molecule (ICAM) RNA sequence comprising SEQ ID NO: 439 in item c). Accordingly, this rejection is now moot. Withdrawal of the 35 U.S.C. § 112, second paragraph, rejection of the aforementioned claims is in order and is respectfully requested.

Rejection of Claims 1-31 Under 35 U.S.C. § 112, first paragraph

Claims 1, 3, 10-21, 30, and 31 stand rejected under 35 USC § 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Office alleged that "written description support does not exist for siRNAs or any other double stranded nucleic acid complementary to a human huntingtin (ICAM) sequence corresponding to SEQ ID NO: 439," and "[i]n fact the term 'huntingin' is not found at all." Office Action, at page 6. As discussed above, claim 1 has been amended so that it no longer recites "a human huntingin (ICAM) nucleotide sequence comprising SEQ ID NO: 439," instead, it recites "a human

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intercellular adhesion molecule (ICAM) RNA sequence comprising SEQ ID NO: 439 in item c).. Accordingly, this rejection is now moot and its withdrawal is respectfully requested.

Priority

The Office has acknowledged Applicant' priority claim but alleged that "[w]hile support is found for claims to chemically modified double stranded nucleic acids complementary to NM_000201, ... support does not exist in prior filed application 60/363,124 for the amended claims" in the prior submission, for reasons given in the rejection under 35 U.S.C. § 112, first paragraph. As illustrated above in the discussion regarding the rejection under 35 U.S.C. § 112, first paragraph, claim 1 has been amended so that support for it can certainly be found in 60/363,124 (the '124 application). Accordingly, Applicant submits that the present claims are entitled to priority of the '124 application.

Rejections of Claims Under 35 U.S.C. § 103(a)

Claims 1, 3, 10-21, 30, and 31 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Bennett et al. (U.S. Patent No. 6,111,094); Agrawal et al. (WO 94/01550); Matulic-Adamic et al. (U.S. Patent No. 5,998,203); and GenBank Accession No. NM_000201. Applicant respectfully traverses this rejection.

It has been established that the Office bears the initial burden of establishing a *prima facie* case of obviousness. *See In re Piasecki*, 745 F.2d 1468, 1472 (Fed. Cir. 1984). To carry this burden, the Office must step back in time and into the shoes of the hypothetical person of ordinary skill in the art just prior to when the inventor made the invention in question. *See* MPEP 2142. Specifically, the Office is required to establish that the references, when combined, teach or suggest all the claim limitations. *See* MPEP 2143; *see also In re Wilson*, 424 F.2d 1382, 1385 (C.C.P.A. 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art."). The Office is further required to establish that there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine the teachings in the references. *See* MPEP 2143; *see also Karsten Mfg. Corp. v. Cleveland Gulf Co.*, 242 F.3d 1376, 1385 (Fed. Cir. 2001). Moreover, the Office bears the burden of establishing that the proposed modifications in the references give a reasonable expectation of success to a skilled

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artisan at the time the invention was made. *See* MPEP 2143; *see also Amgen, Inc., Chugai Pharm. Co.*, 927 F.2d 1200, 1209 (Fed. Cir. 1991).

Applicant takes the position that there is no *prima facie* case of obviousness for the present claims over Bennett in view of Agrawal, Matulic-Adamic, and GenBank Accession No. NM_000201, because the cited references do not, alone or in combination, teach or suggest each and every limitation of the instant claims, and because those skilled in the art would not have been motivated to combine the cited references or have found the requisite expectation of success.

a. References alone or in combination do not teach each and every limitation of the claims.

As the Court of Appeals for the Federal Circuit recently held in *Takeda Chemical Industries v. Alphapharm* (2007 WL 1839698 (Fed. Cir. June 28, 2007)), in addition to the "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise," a *prima facie* case of obviousness also requires "a showing of 'adequate support in the prior art' for the change in structure." *Id.* at page 9 (quoting *In re Grabiak*, 769 F.2d 729, 731-32 (Fed. Cir. 1985)). The Court further held that "a showing that the 'prior art would have suggested **making the specific molecular modifications necessary** to achieve the claimed invention' [is] also required." *Id. (emphasis added)* (quoting *in re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995) and citing *In re Jones*, 958 F.2d 348 (Fed. Cir. 1992); *In re Dillon*, 919 F.2d 688 (Fed. Cir. 1990); *Grabiak*, 769 F.2d 729; *In re Lalu*, 747 F.2d 703 (Fed. Cir. 1984)). Applicants submit that the cited references, by failing to teach or suggest every limitation, alone or in combination, do not suggest making the specific molecular modifications as claimed and cannot render the present claims obvious.

Here, none of the cited references teach or suggest a double stranded nucleic acid molecule that "comprises a sense strand and a separate antisense strand." Moreover, none of the references teach or suggest such a double-stranded nucleic acid molecule having "independently 18 to 27 nucleotides" in each strand. Furthermore, none of the references teach or suggest the claim limitation "about 50 to 100 percent of the nucleotides in the sense strand and about 50 to 100 percent of the nucleotides in the antisense strand are chemically modified with" the specified

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modifications, let alone the limitation that one or more 2'-O-methyl purines are present in the same molecule as one or more 2'-deoxy-2'-fluoro pyrimidines.

Specifically, the Office alleged that "Bennett et al. taught antisense oligonucleotides targeted to human ICAM 1." *See* Office Action, at page 9. The Office further alleged that, according to Bennett, "it has been hoped that inhibitor of ICAM-1 would provide a novel therapeutic class of anti-inflammatory agents." *See id.* Moreover, Bennett allegedly taught that "antisense compounds may comprise from about 8 to about 30 nucleobases, and may be chemically modified with one or more sugar, nucleobase, and/or internucleotide linkage modification at one or more positions within the sequence to enhance the stability and/or activity of the antisense oligonucleotide, including ... 2'-O-methyl and 2'-fluoro modifications. (col.6, and cols. 8-10)." *See* Office Action, at page 10. The Office admits, however, that Bennett does not teach double stranded antisense oligonucleotides targeted to SEQ ID NO:439 or oligonucleotides thereof that contain inverted abasic moieties. *See id.*

Having taught only an antisense molecule, which is a known single-stranded molecule, Bennett could not have taught or suggested items a), b), d), e), or f) in instant claim 1. Moreover, Bennett teaches certain features of antisense molecules, but makes no mention as to whether such features of antisense molecules may be applicable to other types of oligonucleotides.

Agrawal was relied on for allegedly teaching self-stabilized, hairpin antisense nucleotides comprising a target hybridizing region and a self-complementary region that forms a totally or partially double stranded structure. *See* Office Action, at page 10 (citing Agrawal, at page 8, lines 7-15, and page 15, lines 1, to page 16, line 4). Applicant respectfully notes that the self-complementary regions of Agrawal are connected through a non-nucleotide linker, and, as such, are not "separate," in direct contrast with the herein claimed nucleic acid molecule, which comprises a sense strand a **separate** antisense strand. Indeed, Applicant's disclosure strikes a clear line between nucleic acid molecules that have a sense strand and an antisense strand that are "separate" and those nucleic acid molecules wherein the strands are self-complementary and linked by a nucleic acid-base or non-nucleic acid-base linker molecule:

> The siNA can be assembled from two separate oligonucleotides, where one strand is the sense strand and the other is the antisense strand, wherein the antisense and

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> sense strands are self-complementary. . . . Alternatively, the siNA is assembled from a single oligonucleotide, where the self-complementary sense and antisense regions of the siNA are linked by means of a nucleic acid based or non-nucleic acid-based linker(s).

See, e.g., Specification, at page 69, line 29, to page 70, line 8. Along those lines, the instant application also teaches that:

> The siNA molecules of the invention can also be synthesized via a tandem synthesis methodology as described in Example 1 herein, wherein both siNA strands are synthesized as a single contiguous oligonucleotide fragment or strand separated by a cleavable linker which is subsequently cleaved to provide separate siNA fragments or strands that hybridize and permit purification of the siNA duplex. The linker can be a polynucleotide linker or a non-nucleotide linker.

See specification, at page 100, lines 13-18. The specification thus clearly makes a distinction between sense and antisense strands that are "separate" and those that are joined by a linker. The claims recite that the strands are separate, *i.e.*, not joined by a linker. Therefore, Agrawal does not teach a method that employs nucleic acid molecules with a sense strand and a separate antisense stand **as recited in the instant claims**, for example, in items a) and b) of claim 1. Moreover, Agrawal fails to teach nucleic acid molecules of 18 to 27 nucleotides in length, and that "an 18 to 27 nucleotide sequence of the antisense strand of the nucleic acid molecule [being] complementary to a human ... (ICAM) RNA sequence comprising SEQ ID NO: 439," as specifically recited in claim 1, item c). Accordingly, at the very least, Agrawal fails to teach items a), b) and c) of instant claim 1.

The Examiner relied on Matulic-Adamic for allegedly teaching a terminal cap moiety at the 5'-end, 3'-end or both ends, including an inverted deoxyabasic moiety. *See* Office Action, at page 12. Specifically, the Examiner stated that "Matulic-Adamic et al. ... teach a double stranded structure comprising separate sense and antisense strands and further wherein this structure comprising separate sense and antisense strands and further wherein this structure comprises a connecting loop comprising a linker or non-nucleotide linker." *See id.*

However, Matulic-Adamic teaches chemical modification of **ribozymes**, which is known to be substantially single-stranded and which requires at least one stem-loop structure for activity. As such, Matuclic-Adamic does not in any way suggest applying its teachings to double-stranded nucleic acid molecules as are presented claimed, contrary to the Examiner's contentions otherwise. Indeed, at the time of Matulic-Adamic, siRNA and RNA interference

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technology were not known. Matulic-Adamic does not contemplate siRNA or RNA interference, and certainly does not contemplate anything beyond the terminal caps, which by definition cannot constitute a level of chemical modification that is about "50 to 100 percent" in a nucleic acid molecule that is 18 to 27 nucleotides long. Accordingly, Matulic-Adamic does not, alone or in combination with the other cited references, teach any limitation of instant claim 1.

The Office relied on GenBank Accession Number NM_000201 ("GenBank") for allegedly teaching the sequence of human interacellular adhesion molecule (ICAM) gene. However, GenBank does not teach any chemically modified siNA comprising a sense strand and antisense strand as presently claimed. Furthermore, GenBank is completely silent with respect to any siNA, much less chemically modified siNA, let alone one that is differentially modified in the specific pattern as recited in the instant claims. Just like the disclosure of a gene sequence associated with a disease state does not render a subsequently discovered inhibitor (chemical or biological) obvious, mere disclosure of the ICAM gene sequence is not a teaching or suggestion of chemically modified siNA. The connection is simply too tenuous.

Therefore, the pending claims are not rendered obvious in light of the cited references, either alone or in combination, because these references fail to teach each and every element of the claims.

b. There is no motivation or reasonable expectation of success in combining or modifying the cited references.

Applicant further submits that antisense art, on which at least two of the four cited references are based, and the ribozyme art, on which at least one other cited reference is based, all squarely outside the realm of the siRNA art, and teachings or suggestions therein cannot and should not be used as basis for an obviousness rejection against claims directed to siRNA molecules such as those in the instant application. It is established law that any reference or general knowledge cited to demonstrate obviousness must be analogous art. *In re Oetiker*, 977 F.2d 1443, 1447 (Fed. Cir. 1992). The reference must either be in the field of Applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." *Id.*

Initially, Applicant submits that antisense technology is fundamentally a hybridization-based technology, suppressing expressions of certain genes by hybridizing single-stranded

nucleotides to the target mRNAs. In dramatic contrast, siRNA technology at its core involves catalytic degradation of mRNAs, and engages naturally-existing gene suppression mechanisms in biological organisms. At the time of the present invention, while little was known about siRNAs, antisense molecules, the existence of which preceded the siRNA technology by over ten years, were known to be substantially single-stranded, while siRNAs were known to be almost completely in a duplex form. It was also well known to those skilled in the art that single-stranded nucleic acid is more susceptible to nuclease attack than is double-stranded nucleic acid. It was further known that antisense molecules will tolerate substantial 5' and 3' terminal modifications, such as, for example, those described by the cited Bennett reference. *See, e.g.*, Bennett, at col. 10, lines 60 to 66 ("Other preferred modifications include 2'-methyoxy (2'-O-CH_3), 2'-aminopropoxy (2'-$OCH_2CH_2CH_2NH_2$) and 2'-fluoro (2'-F). Similar modifications may also be made at other positions on the oligonucleotide, particularly the 3'-position of the sugar on the 3'-terminal nucleotide or in the 2'-5' linked oligonucleotides and the 5' position of the 5' terminal nucleotide"); and at column 11, lines 12-15 ("Additional modifications may also be made at other positions on the oligonucleotide, particularly the 3' position of the sugar on the 3'-terminal nucleotide and the 5'-position of the 5' terminal nucleotide."). In contrast, the activities of siRNAs are abolished or almost abolished by attaching modifications to the 5' end of the antisense strand of the siRNA. It was further known at the time that the activity of an antisense molecule is destroyed by modifications that alter the DNA-like structure at the core of molecule. These differences, plus the fact that antisense oligonucleotides function in the nucleus, but RNAi activity takes place in the cytoplasm, would certainly have convinced those skilled the art that, to suppress gene expression via RNA interference, siRNA molecules must take on distinct chemical structures from those of antisense oligonucleotides. At the time immediately prior to the present invention, there was no way of telling whether the siRNA duplex would need to maintain an RNA-like structure, whether chemical modifications (what type(s), and/or to what extent) would be tolerated at all, or whether other structures would be permitted for activity.

Likewise, ribozymes fall within a non-analogous art. Specifically, at the time of the present invention, ribozymes were known to be substantially single-stranded prior to interacting with their targets, in direct contrast with siRNAs, which are almost completely in duplex form. As explained above, it is well known at the time that single-stranded nucleic acid is more susceptible to nuclease attack than is double-stranded nucleic acid. Additionally, ribozymes

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were known to tolerate substantial 5' and 3' terminal modifications, again in direct contrast with siRNA molecules, whose activity is abolished or nearly abolished as a result of blocking the 5'-terminal of the antisense strand. Moreover, it was known that ribozymes depend heavily on the formation of a complex RNA secondary structure requiring at least one stem loop structure for activity. These differences, plus the fact that ribozymes, like antisense nucleotides, function in the nucleus where as RNAi activity occurs in the cytoplasm, would not have motivated those skilled in the art to apply any teachings in the ribozyme art. Accordingly, even assuming, *arguendo*, that the cited references in the antisense art and the ribozyme art teach or suggest each and every element of the pending claims, a contention to which Applicant has strongly traversed above, those skilled in the art would not have looked for the motivation to develop the claimed siRNA molecules therefrom.

Because of the known differences in mechanisms, those of ordinary skill in the art would have anticipated that different structural features would be required for activities in siRNA versus ribozymes, and/or antisense nucleotides. Accordingly, they had no basis of predicting the effect of various types and positions of chemical modifications on the activity of a double stranded nucleic acid molecule as claimed herein, let alone the expectation of success.

In fact, contrary to the Office's contention, extensive evidence suggests that highly modified double-stranded siRNA nucleic acid constructs were disfavored in the art at the time of the present invention. In the time period of about 2000-2001, the high potency of siRNAs and the relative stability of the double-stranded structure (as compared to antisense molecules and ribozymes) tended to suggest that no additional chemical modification of the siRNA molecules would be necessary. Evidence that those skilled in the art held such a view can be found in, for example, Elbashir I (EMBO Journal, 20:6877-6888 (2001)) and Tuschl (U.S. Patent Publication No. 2002/0086356), (both of record) where an emphasis was placed on modifying the 3' single stranded ends of the siRNA, with little effort made to modify the double-stranded 5'-ends. *See, e.g.*, Elbashir I, at page 6881, under "2'-deoxy- and 2'-O-methyl-modified siRNA duplexes;" and page 6884, under "Sequence effects and 2'-deoxy substitutions in the 3'-overhang."

Therefore, no motivation or reasonable expectation of success existed at the time of the invention to target ICAM using nucleic acid molecules comprising a sense strand and a separate antisense strand, extensively chemically modified with various chemical modifications, and in particular, comprising one or more 2'-O-methyl purine and one or more 2'-fluoro pyrimidine

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modifications.

For at least the reasons discussed above, the cited references, alone or in combination, do not render the pending claims *prima facie obvious*. Accordingly, withdrawal of the 35 USC §103(a) rejection of the claims based on Bennett, Agrawal, Matulic-Adamic and/or GenBank is in order and is respectfully requested.

Conclusion

In view of the foregoing amendments and remarks, Applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the Examiner believes a teleconference will advance prosecution, he is encouraged to contact the undersigned at the telephone number below.

Date: Aug. 28, 2007

Respectfully submitted,

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